

Observations on Serial Plasma Citrulline Concentrations in a Patient With Intestinal Ischemia and Full-Thickness Necrosis After Severe Thermal Injury

To the Editor:

Recent critical care literature by Piton et al^{1,2} has demonstrated that plasma citrulline may be a helpful adjunct in determining prognosis as well as determining intestinal dysfunction and failure. Citrulline is an amino acid produced by mitochondria within small bowel enterocytes. Citrulline is not incorporated into any protein, its plasma concentration is entirely derived from enterocyte production, and it is metabolized by the kidneys to arginine. Decreased plasma citrulline levels correlate with loss of enterocyte mass in short bowel syndrome and are associated with poor outcomes in radiation enteritis, sepsis, and critical illness.^{1,3,4} We compared their findings with our own recent observations of serial plasma citrulline levels in a severely burned adult who ultimately died from nonocclusive mesenteric ischemia leading to full-thickness small bowel necrosis.

Our patient was a 19-year-old man who sustained burns to approximately 90% TBSA from self-immolation. His 24-hour fluid resuscitation requirements totaled 31,130 mL of lactated Ringer's, 1,100 mL of 5% albumin, and 1,200 mL of fresh frozen plasma. The patient's postinjury course was complicated by burn shock necessitating infusion of norepinephrine (see Figure 1) and vasopressin (0.04 units/min from postburn hour 3 until death) and acute kidney injury (Acute Kidney Injury Network criteria stage 3) treated with continuous venovenous hemofiltration.⁵ Enteral nutrition was provided via nasogastric tube from postburn hours 28 to 39. At postburn hour 42, the patient developed a nonperfusing rhythm and cardiopulmonary resuscitation was initiated. Prompted by elevated lactate levels, emergent laparotomy

was performed revealing necrosis of the entire small bowel (Figures 2 and 3). Further attempts at resuscitation were deemed futile and the patient expired approximately 43 hours after sustaining thermal injury. Plasma was extracted from stored blood samples drawn at postburn hours 19, 24, 34, and 40, and citrulline concentrations were measured using a Beckman 6300 Amino Acid Analyzer (Beckman Coulter, Inc., Fullerton, CA).

The initial citrulline value of 27 $\mu\text{mol/L}$ obtained at postburn hour 19 does not seem concerning based on recent data from Piton et al.² In this group's prospective, observational study on critically ill adults, a citrulline value of 10 $\mu\text{mol/L}$ or lower at 24 hours after intensive care unit admission was an independent predictor of 28-day mortality. What is striking in our patient is the marked, acute decline in plasma citrulline levels to a nadir of 14 $\mu\text{mol/L}$ over the following 21 hours. This absolute decrease of 13 $\mu\text{mol/L}$ in 21 hours is greater than the absolute decline in the mean citrulline level of 9.1 $\mu\text{mol/L}$ over 48 hours in nonsurvivors as reported by Piton et al.² Could the rate of decline in citrulline and its temporal association with small intestinal necrosis potentially indicate that the change in plasma citrulline concentrations, as opposed to an absolute value, is a more helpful indicator of intestinal dysfunction and failure?

The patient demonstrated profound burn shock with a peak norepinephrine requirement of 50 $\mu\text{g/min}$ at postburn hour 18. This was associated with evidence of hypoperfusion and anaerobic metabolism with highest serum lactate of 10.3 mmol/L at hour 21. Despite amelioration of norepinephrine requirements by postburn hour 21, the patient demonstrated persistently elevated serum lactate levels (normal range 0.5–2.2 mmol/L), evidence of continued subclinical shock. After massive thermal injury, our patient's citrulline concentrations appear to be negatively correlated with serum lactate levels (Figure 2). This finding is consistent with the recent report by Piton et al² demonstrating that shock was associated with a decline in plasma citrulline.

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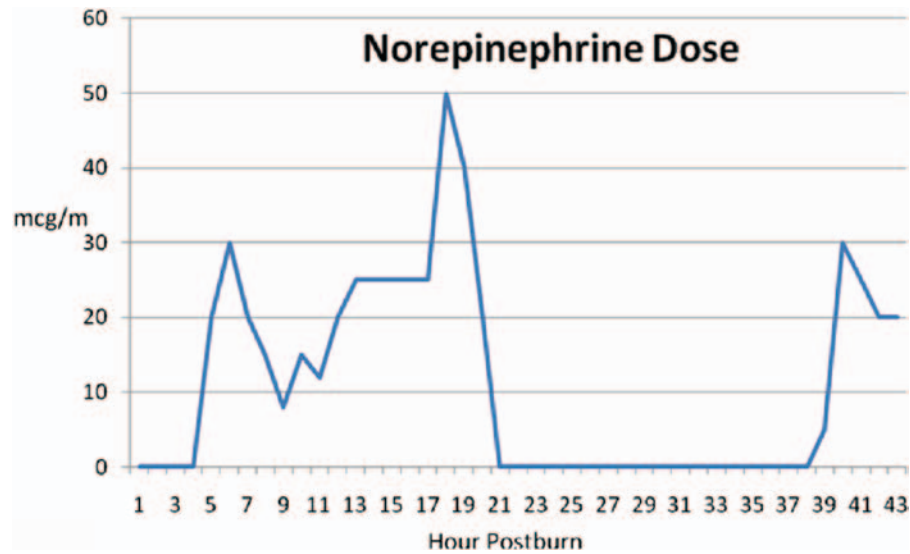


Figure 1. Norepinephrine dosing requirements ($\mu\text{g}/\text{min}$) during hospital course.

Based on periods of relative hemodynamic stability and adequate resuscitation, the patient received enteral nutrition during a portion of his hospital course (postburn hours 28–39). Our burn center recently reported a rate of intestinal ischemia of 1.7% over a 5-year period.⁶ Early use of enteral nutrition has been suggested as a cause of bowel ischemia after severe burns, and its safety in patients with hemodynamic instability has not been well established.^{6,7} The risk relates to the fact that gut mucosa is quite sensitive to ischemia, and the addition of macronutrients to the already stressed enterocyte may unfavorably

tip the scales in an already precarious oxygen supply/demand environment.^{8,9} Could stable serial plasma citrulline levels be an indicator of adequate small bowel perfusion during hemodynamic instability, with a sharp decline indicating a decline in gut perfusion, enterocyte mass loss, and a need for temporary discontinuation of enteral nutrition?

A clear definition of intestinal dysfunction and failure and its association with prognosis in critical illness is needed.¹ The system used to define dysfunction of the alimentary tract would ideally encompass all aspects of its function including motility, absorptive and barrier

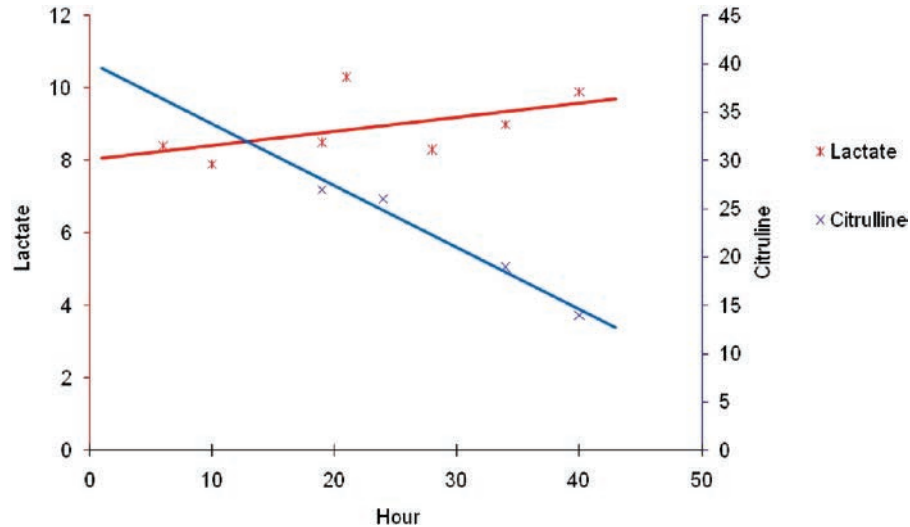


Figure 2. Serum lactate levels (mmol/L) obtained at postburn hours 6, 10, 19, 21, 28, 34, and 40 and plasma citrulline concentrations ($\mu\text{mol}/\text{L}$) obtained at postburn hours 19, 24, 34, and 40.



Figure 3. Findings at laparotomy; small bowel ischemia with full-thickness necrosis.

functions, and endocrine/peptide kinetics. Citrulline remains a promising marker for assisting with a unified definition in critical illness and in our patient showed a marked decline before the diagnosis of the most severe form of intestinal failure: acute necrotizing enterocolitis. Realizing that no single patient's condition can be used to define the utility of citrulline as a marker of intestinal dysfunction, our group is currently examining ways to determine the correlation between plasma citrulline levels in patients sustaining thermal and traumatic injuries and their clinical outcomes.

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